



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Oral Anticoagulation in patients with non-valvular atrial fibrillation and a CHA2DS2-VASc score of 1

a current opinion of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Council on Stroke

Sulzgruber, Patrick; Wassmann, Sven; Semb, Anne Grete; Doehner, Wolfram; Widimsky, Petr; Gremmel, Thomas; Kaski, Juan Carlos; Savarese, Gianluigi; Rosano, Giuseppe M C; Borghi, Claudio; Kjeldsen, Keld; Torp-Pedersen, Christian; Schmidt, Thomas Andersen; Lewis, Basil S; Drexel, Heinz; Tamargo, Juan; Atar, Dan; Agewall, Stefan; Niessner, Alexander

Published in:

European Heart Journal - Cardiovascular Pharmacotherapy

DOI (link to publication from Publisher):

[10.1093/ehjcvp/pvz016](https://doi.org/10.1093/ehjcvp/pvz016)

Publication date:

2019

Document Version

Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Sulzgruber, P., Wassmann, S., Semb, A. G., Doehner, W., Widimsky, P., Gremmel, T., Kaski, J. C., Savarese, G., Rosano, G. M. C., Borghi, C., Kjeldsen, K., Torp-Pedersen, C., Schmidt, T. A., Lewis, B. S., Drexel, H., Tamargo, J., Atar, D., Agewall, S., & Niessner, A. (2019). Oral Anticoagulation in patients with non-valvular atrial fibrillation and a CHA2DS2-VASc score of 1: a current opinion of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Council on Stroke. *European Heart Journal - Cardiovascular Pharmacotherapy*, 5(3), 171–180. [pvz016]. <https://doi.org/10.1093/ehjcvp/pvz016>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

Oral Anticoagulation in patients with non-valvular atrial fibrillation and a CHA₂DS₂-VASc score of 1 – a current opinion of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Council on Stroke

Patrick Sulzgruber¹, Sven Wassmann², Anne Grete Semb³, Wolfram Doehner^{4,5}, Petr Widimsky⁶, Thomas Gremmel^{1,7}, Juan Carlos Kaski⁸, Gianluigi Savarese⁹, Giuseppe M.C. Rosano^{10,11}, Claudio Borghi¹², Keld Kjeldsen^{13,14}, Christian Torp-Pedersen^{15,16}, Thomas Andersen Schmidt¹⁷, Basil S. Lewis^{18,19}, Heinz Drexel^{20,21}, Juan Tamargo²², Dan Atar²³, Stefan Agewall²³, Alexander Niessner¹

Affiliations:

1. Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Austria
2. Cardiology Pasing, Munich, Germany; and University of the Saarland, Homburg/Saar, Germany
3. Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
4. Department of Cardiology (Virchow Klinikum), German Centre for Cardiovascular Research (DZHK), Berlin
5. BIH Center for Regenerative Therapies (BCRT), Charité Universitätsmedizin Berlin, Germany
6. Cardiocenter, Third Faculty of Medicine, Charles University, Prague, Czech Republic
7. Department of Internal Medicine, Cardiology and Nephrology, Landeskrankenhaus Wiener Neustadt, Wiener Neustadt, Austria
8. Molecular and Clinical Sciences Research Institute, St George's, University of London, London, UK
9. Department of Medicine, Cardiology Division, Karolinska Institute, Karolinska University Hospital Solna, Stockholm, Sweden
10. IRCCS San Raffaele Roma, Italy
11. St George's Hospitals NHS Trust University of London
12. Atherosclerosis Research Unit, Medical and Surgical Sciences Department, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
13. Department of Cardiology, Copenhagen University Hospital (Hvidovre-Amager), Copenhagen, Denmark
14. Department of Health Science and Technology, The Faculty of Medicine, Aalborg University, Aalborg, Denmark
15. Department of Health Sciences and Technology, Aalborg University, Aalborg, Denmark.
16. Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.
17. Emergency Department, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark
18. Lady Davis Carmel Medical Center, Haifa, Israel
19. Technion-Israel Institute of Technology, Ruth and Bruce Rappaport School of Medicine, Haifa, Israel
20. VIVIT Research, Landeskrankenhaus Feldkirch, Austria
21. Private University of the Principality of Liechtenstein, Principality of Liechtenstein
22. Department of Pharmacology and Toxicology, School of Medicine, Universidad Complutense, Madrid, Spain
23. Department of Cardiology, Oslo University Hospital and Institute of Clinical Medicine, Oslo University, Oslo, Norway

Short title: Anticoagulation in patients with a CHA₂DS₂-Vasc of 1

Word count: 4743

Number of figures: 1

Number of tables: 1

Correspondence:

Assoc.-Prof. Priv.-Doz. Dr. Alexander Niessner, MSc, FESC

Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna,
Währinger Gürtel 18-20, 1090 Vienna, Austria,

E-Mail: alexander.niessner@meduniwien.ac.at

Phone: +4314040046140

Fax: +4314040042160

Keywords: anticoagulation, atrial fibrillation, CHA₂DS₂-VASc score, intermediate risk

Oral anticoagulation in Atrial Fibrillation

Non-valvular atrial fibrillation (AF) represents the most common arrhythmia in clinical practice, currently affecting more than 8 million people independently in Europe. (1) AF confers a substantially increased risk for thromboembolic events and is responsible for more than 26% of all diagnosed ischemic strokes that are often lethal or severely disabling. In the western world, AF is currently diagnosed in more than 3% of the adult population without extrapolating the estimated undiagnosed/silent AF cases. (2) As a major future healthcare burden, AF prevalence increases dramatically after the age of 60 years and the ageing society fuels further the epidemic of AF in the next decades according to demographic forecasts. (3-4) While the therapeutic approach of AF consists of a multifaceted interaction of rate control, rhythm control and antithrombotic therapy, it is well recognized that the most beneficial independent management decision in those individuals concerns the issue of stroke prevention. (5)

Since oral anticoagulation (OAC) effectively prevents the majority of ischemic strokes in AF, simple schemes for stratification of patients' individual risk for stroke were already developed in the 1990s based on small cohort studies resulting in the CHADS₂ score as a valid tool for prediction of thromboembolic events. (6) However, the CHADS₂ score was not sensitive at its lower scoring range for thromboembolic risk. In the 2010 update of the guidelines on the management of AF of the European Society of Cardiology (ESC), the CHADS₂ score was replaced by the CHA₂DS₂-VASc score, which is, until now, recommended to assess the risk of stroke in AF. (5, 7) The more sensitive CHA₂DS₂-VASc score covers the variables congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus type II, previous stroke/transient ischemic attack or thromboembolism, vascular disease, age 65-74 years and female gender. However, other potential risk factors such as impaired kidney function, cancer, rheumatoid arthritis, obesity or smoking were not included in the model.

Guidelines advise initiation of OAC therapy (preferably non-Vitamin K antagonist oral anticoagulants [NOAC] or Vitamin K antagonists [VKA]) in AF patients with a CHA₂DS₂-VASc score ≥ 2 for lowering the individual stroke risk, while an OAC approach in individuals with a CHA₂DS₂-VASc score of 0 is not recommended. (5)

These recommendations pose a gray area for about 15% of patients with a CHA₂DS₂-VASc score of 1 who may benefit from OAC (8). Although the ESC Guidelines on the management of AF state that OAC in individuals with a CHA₂DS₂-VASc score of 1 might prevent thromboembolic events, serious bleeding complications, as the major downside of OAC, may outweigh these benefits.

Therefore, physicians need to carefully balance the individual *benefit* of reducing thromboembolic risk with OAC against the potential *harm* due to an increase in bleeding risk in this intermediate-risk patient population. Consequently, stroke prevention in patients with a CHA₂DS₂-VASc of 1 (CHA₂DS₂-VASc of 2 in women) is a major challenge in clinical practice. Of note, a substantial number of patients is not receiving any OAC before and, even despite increased risk, after a first thromboembolic event. (9) Since we do not have profound data of randomized controlled trials, we need to rely on mainly observational data or even expert opinions to decide whether or not to initiate OAC in AF patients with a CHA₂DS₂-VASc of 1.

The Net-Benefit of Oral Anticoagulation – Stroke Prevention vs. Bleeding Risk

The risk of stroke is not homogeneous in patients with AF and strongly varies depending on age, comorbidities and also among populations. (8-10) However, only AF registries that encompass an adequately powered sample size of intermediate-risk patients enable the extension of knowledge regarding risk factors, outcome associations and – most importantly - risk evaluation of different treatment strategies.

There is common consensus that a thromboembolic event rate of 1% per year is needed to justify initiation of OAC in AF. (5, 10-11) As mentioned before, the risk of thromboembolic events in AF is estimated with the CHA₂DS₂-VASc score. The adjusted event rates per year within the respective score classes are displayed in Table 1. Compared to the CHADS₂ score the CHA₂DS₂-VASc score became more sensitive in the lower scoring range. While individuals with a score of 0 have an estimated and adjusted annual stroke risk of approximately 0%, the event rate in AF patients presenting with a CHA₂DS₂-VASc score of 1 is 1.3%. (8-9) Considering a thromboembolic risk of >1% per year in those patients, the initiation of OAC for stroke prevention seems justified. However, data on the adjusted annual stroke risk are very variable and depend on the respective validation cohort. In this regard, data of the Euro-Heart Survey demonstrated an adjusted annual stroke risk of 0.6% in individuals with a CHA₂DS₂-VASc score of 1. (8) As expressed by the 2016 ESC guidelines on the management of AF the three Population, Intervention, Comparison, Outcome and Time (PICOT) questions on relevant topics for the guidelines highlighted the need to investigate ischemic stroke rates in AF patients with a CHA₂DS₂-VASc score of 1 with and without OAC therapy. Thereby, annual stroke rates were not equal across investigated study populations, showing an overall event rate of 1.4% (0.5-2.9) per 100 patient years in intermediate-risk AF individuals receiving no OAC, compared to 0.7% (0.1-1.3) per 100 patient years under OAC. (5, 8-10)

Recent data from a large Swedish registry challenged the current concept of OAC in intermediate-risk AF patients. (12) In 12.298 enrolled participants with a CHA₂DS₂-VASc score of 1, an adjusted event rate of 0.5% to 0.9% was observed although the composite endpoint included transient ischemic attack (TIA), pulmonary embolism (PE), systemic embolism, unspecified stroke and ischemic stroke.

Considering these data, the concept that individuals with a CHA₂DS₂-VASc score of 1 have an adequately high annual risk to merit OAC for stroke prevention needs to be questioned.

Providing an evidence-based approach for filling this gap of knowledge, the patients' individual net clinical benefit seems to be a reasonable decision-making tool for OAC treatment. To assess the net-benefit of OAC in patients with AF and a CHA₂DS₂-VASc score of 1, the risk of thromboembolic events needs to be weighed against the bleeding risk – in particular intracranial bleeding. To estimate annual bleeding risk, the ESC guidelines on the management of AF recommend the use of scoring tools such as the ABC, ATRIA, ORBIT or HAS-BLED scores. (13-15) Since the HAS-BLED score has been validated for both NOAC and VKA use and mirrors an easily assessable scoring tool to elucidate the individual risk of bleeding, that might be used in this regard. (11, 13, 16) A detailed summary of the HAS-BLED score categories and their respective bleeding risks are shown in Table 1.

Especially with VKA, the risk of major bleeding is dependent on the quality of anticoagulation and the patients' adherence and compliance. In individuals reaching a therapeutic target range of an international normalized ratio (INR) between 2.0-3.0 with a recommended continuity of at least 70% of the time, the risk of major bleeding was estimated to be 1.3% per year. (11, 16) The respective bleeding risk associated with the HAS-BLED score classes within the lower range (score ≤1) is between 0.59% and 1.51%. (16-17) In the large landmark phase III trials on NOAC – RE-LY, ARISTOTLE, ENGAGE AF and ROCKET-AF – the risk of bleeding was properly assessed. (18-21) Compared to warfarin, the risk of major bleeding was significantly reduced with dabigatran (only 110mg bid), apixaban and edoxaban, while rates of major bleeding were similar to those observed with VKA in patients receiving high-dose dabigatran (150mg bid) and rivaroxaban. However, intracranial hemorrhage (ICH) still represents the major concern in individuals receiving OAC. While the sequelae of ICH seem to be less severe in patients receiving a NOAC, NOAC also showed a strong reduction in annual ICH rates compared to warfarin with an overall hazard ratio of 0.48 in the above-mentioned major landmark trials. (22) Interestingly, data from the Swedish hospital discharge register

highlighted that the risk of ischemic stroke without VKA is higher than the risk of intracranial bleeding almost irrespective of HAS-BLED und CHA₂DS₂-VASc score categories. While their analysis on the net clinical benefit of VKA indicated a potential benefit in patients with a CHA₂DS₂-VASc score of 1 and a HAS-BLED score of 2, an equality in risk was observed with a HAS-BLED score of 3. However, based on both the low number of endpoints in especially low and intermediate risk individuals and the observed confidence intervals, conclusions on the net clinical benefit that can be drawn from this investigation are limited for AF patients with a CHA₂DS₂-VASc score of 1. (23)

Based on the annual thromboembolic risk of 0.6% to 1.3% and the individual bleeding risk of 0.59% to 1.51%, we are currently not able to draw a conclusion concerning the net benefit of OAC in patients with both a CHA₂DS₂-VASc and HAS-BLED score of 1. Considering annual bleeding rates of 1.88% to 3.20% per year in patients presenting with a HAS-BLED score of 2, the annual risk of bleeding outweighs the thromboembolic risk associated with a CHA₂DS₂-VASc score of 1, which amounts to only 0.6% to 1.3% per year. (Table 1) Therefore, OAC should not be considered in intermediate thromboembolic risk patients with a HAS-BLED score ≥ 2 . To elucidate a potential treatment benefit of OAC in CHA₂DS₂-VASc score of 1, a refinement of risk estimation in individual thromboembolic and bleeding risk is needed.

Refinement of Individual Thromboembolic Risk

Do all Thromboembolic Risk Factors Count Equally?

Considering the clinical application of the CHA₂DS₂-VASc score, it covers the following easily available patient characteristics for the assessment of the adjusted thromboembolic risk in patients with AF: (5)

- congestive heart failure (1 point)
- hypertension (1 point)

- age >75 years (2 points)
- type II diabetes mellitus (1 point)
- stroke/TIA (2 points)
- vascular disease (1 point)
- age 65-74 years (1 point)
- female gender (1 point)

Weighing of individual risk factors: The score itself gives one scoring point for each present risk factor – except previous stroke/TIA and age above 75 years (with 2 points each). This weighing was chosen basically for practical reasons in order to make the scoring tool clinically useful and simple to apply at bedside. (5) However, data from China challenged this practical “1-point”-concept of risk estimation in the subgroup of patients with a CHA₂DS₂-VASc score of 1 by showing a different individual increase of thromboembolic risk depending on the particular risk factor. (24) This effect remained evident after stratification in male and female individuals. The most prominent risk increase was observed for “age 65-74years” followed by “type II diabetes mellitus”. However, AF patients presenting with diabetes mellitus type 1 aged below 65 years were found to be at lower risk for thromboembolic events compared to their type II diabetes mellitus counterparts. (25) The effect of a well-controlled type II on the individual thromboembolic risk remains unknown and needs to be addressed in future investigations.

The lowest risk for stroke was evident in “hypertension” for female and “vascular disease” for male patients. Of note, the average annual risk of ischemic stroke in this analysis was 2.75% per year and therefore higher as reported in previous analyses on this topic.

Exceptional position of female gender: Female gender has previously been suggested as a potential risk factor for thromboembolic events in patients with AF and has therefore been

included in the CHA₂DS₂-VASc score and the respective guidelines. (26-27) However, using the CHA₂DS₂-VASc score, it needs to be considered that female gender is not an isolated risk factor per se – it only counts for risk estimation in presence of an additional risk factor. Data of a large national Danish registry illustrated risk discrimination of male and female AF patients. (28) The registry yielded an annual risk for thromboembolic events that was comparable between male and female individuals below 75 years of age; only in patients equal or above 75 years female gender was associated with an increased risk of thromboembolism compared to their male counterparts. These results suggest that female gender should not be implemented in risk estimation without careful prior consideration of the patients' age. Importantly, the patients' age (>65 years) conveys a strong and continuously increasing risk for thromboembolic events in female and male patients that also potentiates other risk factors used in the CHA₂DS₂-VASc score. (29-30)

Definition of Risk Factors

In addition to the aforementioned concerns regarding the variables included in the CHA₂DS₂-VASc score, the definitions of the risk factors – which may influence the estimation of the individual thromboembolic risk – might need to be reconsidered. This is of particular importance for the definitions of “congestive heart failure” and “hypertension”.

Congestive heart failure: In large registries on AF, the presence of congestive heart failure is only defined as the presence of heart failure-associated symptoms (predominantly defined by the New York Heart Association [NYHA] classification), which may also include patients with heart failure with preserved ejection fraction (HFpEF). Moreover, the current definition does not reflect whether left ventricular ejection fraction (LVEF) is severely reduced or might be influenced by a recent decompensation. Similarly, information about the prognostic impact of a transient reduction of LVEF – possibly tachycardia-induced – with a subsequent recovery of

symptoms remains scarce. In this regard recent data demonstrated that patients with stable heart failure (detected by low N-terminal pro-B-type natriuretic peptide values) did not appear to be at risk of thromboembolic events. (31) Similar results were evident for individuals presenting with a well-controlled hypertension. (32)

Hypertension: There is no evidence in literature concerning the definition of hypertension as a cardiovascular risk factor. Usually the presence of hypertension is defined as the history of hypertension (including anti-hypertensive treatment at the time of assessment). Since it seems intuitive that it has a strong impact on the discriminatory power of the CHA₂DS₂-VASc score, it might be of utmost importance to investigate whether well-controlled hypertension has the same predictive value for thromboembolic events in AF as not adequately controlled hypertension.

A clear definition of both congestive heart failure and hypertension within the CHA₂DS₂-VASc score seems crucial for a proper assessment of the actual thromboembolic risk – especially in intermediate-risk individuals. While there is a major need for future investigations in this field, it has currently no consequence in terms of the initiation of OAC.

Consideration of Additional Risk Factors

Facing the scenario of a CHA₂DS₂-VASc score of 1, the use of additional risk factors which may help to stratify patients with potential OAC-benefit needs to be considered. These variables might include data on *lifestyle* (e.g. tobacco and ethanol abuse) or the patients' *physical appearance* (e.g. obese vs. athletic; dementia). Of note while obesity is a well-established risk factor for thromboembolic events, recent data from Japan reported a low-body weight as a risk factor for stroke in AF patients within the general Japanese population. (33) However, those data might ground on a potential underuse/-dosage of (N)OAC agents, based on a frail appearance of the respective patients as recently described. (34) Additionally, compliance and

adherence of drug intake in patients with dementia might not be reasonable based on a potential under-use or accidental over-dosage. (35) In terms of OAC, it introduces a substantial risk of major bleeding without any consistent risk reduction on thromboembolic events. Therefore, the initiation of an antithrombotic therapy in AF patients with dementia needs to be evaluated with caution based on ethical considerations and the individual nursing care for drug-intake.

The patients' *renal function* seems to be of utmost importance for decision making since it proved to be predictive for the development of thromboembolic events in the general AF population. (36) Similarly, chronic kidney disease was found to be associated with an increased risk of stroke, systemic thromboembolism and also bleeding events among patients with AF. Therefore, the newly developed R₂CHADS₂ or ATRIA scores (both were tailored to predict thromboembolic risk in patients with non-valvular AF) include the variables "proteinuria", "end-stage renal disease" or "estimated glomerular filtration rate (eGFR) of below 45ml/min". (37-38) These variables are useful for weighing the individual thromboembolic risk in intermediate-risk patients and thus can be considered for decision making. However, since patients with "end-stage renal disease" (eGFR of below 15ml/min) mirror a high-risk population, conclusions of the present consensus statement can not be applied to this specific sub-group.

Data of *cardiac imaging* (including echocardiography or cardiac magnetic resonance) might also help to identify patients at risk. Especially data on both the functional und structural status – for example the left atrial appendage emptying velocity (<20cm/s) or fibrosis in the left atrial wall – seem to add discriminatory value. (39-41) Most importantly, an increased left atrial size mirrors an easily assessable diagnostic marker that provides strong discriminatory power of the patients' individual risk for thromboembolic events. (42-43)

However, even if currently no prospective data for validation of these additional risk factors in patients with a CHA₂DS₂-VASc score of 1 are available, it seems advisable to include the above-mentioned characteristics in decision making when considering OAC. Of note, despite an individualized weighing of risk, the *patients' preferences* are a crucial value with regard to the proposed therapeutic OAC concept. This human factor needs to be considered in decision making especially in individuals with a CHA₂DS₂-VASc score of 1 in order to ensure compliance which strongly influences outcome.

Biomarkers and Biomarker-based Risk Scores

Nt-proBNP and Troponin: The 2016 ESC guidelines on the management of AF recommend that the use of biomarkers – in particular N-terminal pro-B-type natriuretic peptide (Nt-proBNP) and cardiac Troponin (high-sensitivity) T and I – should be considered for treatment decisions. (5) This recommendation is based on a recent publication of Hijazi and colleagues that highlighted the additional prognostic value of the measurement of cardiac Troponin and Nt-proBNP for risk stratification in selected (especially low- and intermediate-risk) AF patients. (13) The composite endpoint in the study's investigation was defined as stroke, systemic embolism, pulmonary embolism, myocardial infarction and vascular death (excluding hemorrhagic death). While there was a clear linear trend of increasing risk with increasing troponin values, especially in individuals with a CHA₂DS₂-VASc score of 0 or 1, Nt-proBNP values did not exhibit a clear correlation with an increased risk for thromboembolism. However, initial Nt-proBNP values above 1400ng/l can be considered as significant risk factor as defined by the ABC stroke risk score and recommended by the ESC guidelines on the management of AF. (5, 13)

ABC (Age/Biomarker/Clinical history) Score: The ABC Stroke Risk Score – which covers the variables *age*, *biomarker* (GDF-15, cardiac high-sensitivity Troponin and hemoglobin) and *clinical history of stroke* – may help to further refine the thromboembolic risk of patients with a CHA₂DS₂-VASc score of 1. (30) Using the aforementioned values, the ABC score allows discrimination of the individual risk in annual thromboembolic event rates of <0.3%, 0.3-1.0%, 1.0-2.0% and >2%. This biomarker-based approach may guide the treating physician in decision making in intermediate-risk AF patients with an unclear antithrombotic benefit of OAC.

Type and Symptoms of Atrial Fibrillation

Paroxysmal vs. persistent/permanent AF

A major point in decision making might be the type of AF the respective patient presents with. As evident in current guidelines, OAC should be considered in patients with AF irrespective of the individual AF-type. However, several analyses revealed that patients with permanent AF are at a higher risk of stroke compared to patients with non-permanent AF. This was recently confirmed by a meta-analysis including data of 99,996 patients. (44-45) While permanent AF increased the risk of embolic events by 50–100% in individuals with a CHA₂DS₂-VASc score ≥ 2 , patients presenting with paroxysmal AF still had an annual stroke rate of at least 2%. These data strengthen current recommendations that patients with a high clinical risk of stroke should be anticoagulated regardless of their AF pattern. Of note this analysis included a low number of patients with a CHA₂DS₂-VASc score of 1 (<10%).

Interestingly, a similar investigation revealed annual stroke rates of 0.36% and 1.3% for paroxysmal and permanent AF, respectively, during 10 years of follow-up in young AF patients without additional risk factors. (46) Thus, the pattern of AF may help to quantify the thromboembolic risk in patients with a CHA₂DS₂-VASc score of 1. However, future

investigations in this field are needed in order to elucidate a clear prognostic potential before its clinical application.

Atrial Fibrillation vs. Atrial Flutter

According to current guidelines, patient with atrial flutter (AFL) and AF should both receive OAC in the same manner. Recent data from the Taiwan National Health Insurance Research Database (n=219,416) suggested a strong deviation between the actual thromboembolic risk of AF and AFL. The authors observed that event rates per 100 person-years of both ischemic stroke (AF: 3.1% vs. AFL: 1.5%) and mortality (AF: 17.8% vs. AFL: 13.9%) were significantly higher in AF. These results were also evident in patients with a CHA₂DS₂-VASc score of 1, showing an increased risk for ischemic events (HR: 2.88 [95%CI: 1.73-4.80]) and all-cause mortality (HR: 1.43 [95%CI: 1.23-1.66]) in AF patients compared to AFL individuals. Of note, comparing AFL to non-AF/AFL patients, the authors observed no increased risk for ischemic stroke (HR: 0.90 [95%CI: 0.53-1.54]) but for all-cause mortality (HR: 3.12 (95%CI: 2.63-3.74)). Considering these results, the type of atrial arrhythmia may be considered for refinement of thromboembolic risk in patients with intermediate risk. (47) However, these data need to be confirmed in an independent cohort before drawing any therapeutic conclusions.

Atrial Fibrillation Associated Symptoms

Similarly, the impact of “silent AF” needs to be discussed, since more than one third of AF cases are asymptomatic. Those individuals give the impression to be at a lower risk for both thromboembolic and adverse cardiac events based on their individual clinical presentation. However, there is evidence that the risk of stroke in silent AF is similar to of the risk of symptomatic individuals. In this regard Glotzer et al. revealed that moderately severe AF-related symptoms represent a poor indicator for the presence of AF, having a sensitivity of

82.4% but a specificity of only 38.3%. Based on these observations, AF-related symptoms should not be considered for decision making pro or contra OAC in AF. (47-49)

Of note, a challenging issue in this specific subgroup mirrors the transition from paroxysmal to persistent AF, which is likely to be missed in silent AF patients, but potentially accompanies a strong impact on the individual thromboembolic risk. However, there is no clear evidence available in current literature on the effect of OAC in patients with silent (device detected) AF. However, ongoing trials (ATRESiA trial; NCT01938248) will provide profound data on the antithrombotic management in this low-risk AF population in the near future

Refinement of the Individual Bleeding Risk

Besides thromboembolic risk, the individual risk of bleeding needs be considered when assessing the net-benefit of OAC. Similar to the CHA₂DS₂-VASc score, the HAS-BLED score was established (as a 1 point per risk factor scoring tool) to identify patients at higher risk for bleeding events and still represents the gold standard in bleeding risk estimation using easily available characteristics: hypertension (>160 mmHg systolic blood pressure); renal disease; liver disease; history of stroke; prior major bleeding or predisposition to bleeding; labile INR (in VKA recipients); age >65 years; medication predisposing for bleeding; alcohol use. (8-11)

Of note, the HAS-BLED score was additionally developed to foster a close patient follow-up and draw the physicians' attention to potentially reversible risk factors for bleeding events such as labile INRs (in VKA), uncontrolled hypertension (>160mmHg of systolic blood pressure), or co-medication. A parallel intake of antiplatelet therapy, chronic concomitant use of non-steroidal anti-inflammatory drugs or selective serotonin reuptake inhibitors (SSRIs) and other possible interacting drugs need to be taken into account with regard to an increased bleeding risk – especially gastro-intestinal bleedings. Moreover, kidney and liver function add prognostic value to the individual bleeding risk assessment.

These patient characteristics need to be considered when estimating the individual risk of bleeding and require – if possible – optimization and control when OAC is indicated.

In the era of NOAC the actual bleeding risk estimation might be even more challenging, since the HAS-BLED score is based on patients receiving VKA. However, compared to the ABC or ORBIT score, the HAS-BLED score has subsequently been validated for patients receiving NOAC. (50-52) Since there are currently no other validated alternative prediction tools for risk assessment in this regard, physicians should therefore use the HAS-BLED score for estimation of the individual risk of bleeding. As a future perspective it might be possible to specify bleeding risk estimation via a biomarker-based approach. Growth differentiation factor 15 (GDF-15) has been introduced as a marker that specifically predicts bleeding events, and therefore might be useful for risk stratification in intermediate-risk AF patients in the near future. (30)

Therapeutic Strategies in CHA₂DS₂-VASc of 1

If – after a comprehensive evaluation considering both the individual thromboembolic and bleeding risk – the treating physician decides that the patient with AF and a CHA₂DS₂-VASc score of 1 will benefit from antithrombotic treatment, there are two common therapeutic strategies in clinical practice: antiplatelet therapy (acetylsalicylic acid [ASA]) or OAC using NOACs or VKAs. To provide contemporary clinical guidance, we are able to rely on highly powered observational data and subgroup analysis of recent phase III randomized controlled NOAC landmark trials. (18, 53-64)

ASA vs. VKA: Data on a large nationwide Danish registry indicate a net-benefit for warfarin with regard to the composite endpoint (=ischemic stroke, intracranial hemorrhage, major bleeding and myocardial infarction) compared to ASA and to no treatment in patients with a

CHA₂DS₂-VASc score of 1. Of note, there was no net clinical benefit observed for ASA compared to no treatment. (52)

ASA vs. NOAC: The AVERROES trial represents the first randomized controlled trial on this topic, comparing ASA to apixaban for antithrombotic therapy in patients with AF. (53-54) The study team observed a prominent advantage for reduction of stroke and systemic embolism with apixaban (event rate: 1.6%), compared to ASA (event rate: 3.7%) with a relative risk reduction of 55%. Of note, there was no increased risk of bleeding reported with apixaban (event rate: 1.4% [apixaban] vs. 1.2% [ASA]). However, there was no specific subgroup analysis of patients with a CHA₂DS₂-VASc score of 1.

NOAC vs. VKA: Based on a post-hoc analysis of the RE-LY trial, Eckmann et al investigated the tipping point of OAC in patients with AF within calculations of a decision model. They observed that warfarin was preferred in patients with a stroke rate above 1.7% per year. Interestingly, anticoagulation with NOAC may lead to a lowering of the threshold for OAC use to a stroke rate of 0.9% per year. (55)

With regard to the large phase III NOAC trials, a subgroup analysis for CHA₂DS₂-VASc score of 1 (N=1604) was performed in the ARISTOTLE trial comparing apixaban to warfarin. (18, 56) Considering thromboembolic events (HR: 1.18 [95% CI:0.46-2.98]; p-value for interaction of 0.121), major bleeding (HR: 0.65 [95% CI:0.31-1.37]; p-value for interaction of 0.206) and intracranial hemorrhage (HR: 0.55 [95% CI:0.13-2.29]; p-value for interaction of 0.848), consistent effects were observed for apixaban.

Taking these data into account, it can be speculated that there is a consistent benefit of apixaban compared to warfarin in patients with intermediate-risk AF, although the study was underpowered for the performed subgroup analysis.

Most recently rivaroxaban (n=3319) was found to be associated with a lower rate of both ischemic stroke and systemic embolism (HR 0.41 [95%CI: 0.17-0.98]) without increasing

major bleeding events (HR 0.74 [95% CI: 0.44-1.26]) in AF naïve individuals presenting with a CHA₂DS₂-VASc score of 1 compared to VKA (n=3319). (64)

The Exceptional Position of Coronary Artery Disease: The decision for or against OAC in patients with a CHA₂DS₂-VASc score of 1 with coronary artery disease (CAD) and the indication for single or dual anti-platelet therapy (DAPT) remains challenging. Combining two antiplatelet agents with OAC significantly increases the risk of (major) bleeding most likely outweighing the thromboembolic risk in AF patients without a further risk factor in the CHA₂DS₂-Vasc score. (59-61) In this regard DAPT for 12 months (including clopidogrel and new P2Y₁₂ inhibitors) may be considered as a sufficient antithrombotic regimen for intermediate-risk AF patients with acute coronary syndrome and/or percutaneous coronary intervention (or stent implantation) and AF. However, based on recent studies the combination of an OAC with low bleeding risk and only one anti-platelet therapy may provide an optimized net benefit. However, there are no subgroup analysis available for patients with CHA₂DS₂-VASc score of 1 within these trials. (59-61) Decisions should be made considering the patients' individual atherothrombotic risk after stent implantation via recommended risk scores (REACH or SYNTAX Score if elective; GRACE ≥ 140 if ACS) or patient characteristics (stenting of left main, proximal LAD, proximal bifurcation, recurrent myocardial infarction or stent thrombosis). Moreover, a single episode of AF triggered by AMI may not justify long-term OAC in intermediate-risk patients as the reoccurrence rate of AF remains to be determined. However, the re-occurrence of AF should be screened regularly. One year after stent implantation and/or ACS antithrombotic therapy should be restricted to monotherapy either with an antiplatelet agent or with OAC based on risk refinement for patients with a CHA₂DS₂-Vasc score of 1. If no OAC has been started, the accumulation of additional risk factors for thromboembolic events over time (e.g. age >65 years) needs to be assessed regularly and long-

term therapy should be switched from antiplatelet therapy to OAC if the CHA₂DS₂-Vasc score increases further.

Summary of Evidence on Therapeutic Strategies

Since consistent beneficial effects were observed for NOACs compared to VKAs in terms of thromboembolic and bleeding events in patients with intermediate risk AF, a superior net benefit of NOACs over VKAs can be assumed. Data from the large phase III trials – RE-LY, ARISTOTLE, ENGAGE AF and ROCKET-AF – indicate that major bleeding was significantly reduced with dabigatran (110 mg bid), apixaban and edoxaban, while rates of major bleeding were similar with high-dose dabigatran (150mg bid) and rivaroxaban compared to VKAs. (15-18) Additionally, NOACs showed a strong reduction in annual ICH rates compared to warfarin with an overall hazard ratio of 0.48 in the four trials. (63) Considering these data, NOACs seem to offer a therapeutic benefit with regard to stroke prevention and bleeding risk compared to VKA in this intermediate-risk patient population. (62-64) There are currently no data whether a reduced dosage of NOACs offers a net benefit in these patients when compared to full-dose NOAC and VKA therapies. Observational studies and recent randomized controlled trials highlighted that ASA is not a beneficial treatment option in intermediate-risk individuals. Therefore, ASA should not be considered for stroke prevention in AF patients with a CHA₂DS₂-VASc score of 1 free of CAD. However, intermittent DAPT for one year after stent implantation and/or ACS seems justified in patients with a CHA₂DS₂-VASc score of 1 and a high atherothrombotic risk.

Conclusion

Since the risk of stroke is heterogeneous in individuals with AF and a CHA₂DS₂-VASc score of 1, risk assessment should be carefully performed in the respective patients and further refined

by available predictive tools or biomarker-based approaches. This refinement also comprises additional (cardiovascular) risk factors at the time of presentation and the patients' individual preferences. A personalized decision-making and comprehensive weighing of the respective risk factors seems crucial.

Anti-thrombotic treatment with NOACs seems to offer a superior net benefit with regard to prevention of thromboembolic events and the risk of major bleeding compared to VKAs. It currently provides the most beneficial and reasonable treatment approach in individuals with AF and a CHA₂DS₂-VASc score of 1. Considering data on major bleeding in the phase III trials, NOAC therapy with a low risk of intracranial bleeding should therefore be preferred over VKAs in these patients. Based on current evidence, ASA does not offer any advantage for patients with CHA₂DS₂-VASc score of 1 free of CAD compared to OAC. DAPT for 12 months, including clopidogrel and new P2Y₁₂ inhibitors, may be considered in AF patients with an intermediate thromboembolic but high atherothrombotic risk and an ACS and/or coronary intervention within the last year.

Figure 1 and Table 2 illustrate an evidence-based approach of both risk assessment and antithrombotic therapy in patients with a CHA₂DS₂-VASc Score of 1.

Consensus Statement

- There is currently no evidence from randomized controlled trials to guide anticoagulation in patients with AF and a CHA₂DS₂-VASc score of 1. However, experience from recent observational trials indicates that the thromboembolic risk of AF patients with a CHA₂DS₂-VASc score of 1 might be lower than anticipated. A general recommendation of OAC therapy in these individuals might weaken the net clinical benefit due to an increased risk of bleeding events. Therefore, refinement of the individual thromboembolic risk assessment is needed.

- The HAS-BLED score was established as a clinical risk prediction tool for the occurrence of bleeding events and has been developed in patients receiving VKA therapy. Therefore, the bleeding risk associated with NOAC therapy may be even more difficult to assess. However, its predictive value has recently been validated in several investigations including a representative proportion of individuals receiving NOACs. Considering annual bleeding rates of 1.88% to 3.20% per year in patients presenting with a HAS-BLED score of 2, the annual risk of bleeding outweighs the thromboembolic risk associated with a CHA₂DS₂-VASc score of 1, which amounts to only 0.6% to 1.3% per year. (Table 1) Therefore, OAC should not be considered in intermediate thromboembolic risk patients with a HAS-BLED score ≥ 2 .
- Considering the predictive value of individual markers in both male and female patients, age and diabetes mellitus type II may be the most important isolated risk factors for thromboembolic events. LA size seems a reasonable and easily assessable imaging marker for risk stratification. Routinely available biomarkers such as cardiac troponin (high sensitivity troponin T or I) and Nt-proBNP as well the burden of AF (paroxysmal AF vs. non-paroxysmal AF) may provide additional prognostic information to enhance risk estimation and decision making for OAC particularly in intermediate-risk individuals. Importantly, the patients' individual preference for, or against initiation of OAC must be taken into account.
- Therapeutic decisions should be based on the individual balance between thromboembolic and bleeding risk – the therapeutic preference should be on doing no harm rather than avoiding stroke. If the decision of OAC initiation in AF patients presenting with a CHA₂DS₂-VASc Score of 1 has been made, NOACs with a superior net-clinical benefit should be preferred over VKAs.

- There is no evidence that patients with AF presenting with a CHA₂DS₂-VASc score of 1 (except with CAD) benefit from ASA therapy. Therefore, ASA for stroke prevention should not be considered in this intermediate-risk patient population.
- DAPT for 12 months, including clopidogrel and new P2Y₁₂ inhibitors, may be considered in AF patients with an intermediate thromboembolic risk and an ACS and/or coronary intervention.

Acknowledgements

None

Funding

None

Conflicts of Interest

Patrick Sulzgruber: none; Sven Wassmann: reports personal fees from Bristol Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Pfizer, personal fees from Daiichi Sankyo, outside the submitted work; Anne Grete Semb: received speaker honoraria and/or consulting fee from Lilly, Novartis, AbbVie, Bayer, Roche and Sanofi; Wolfram Doehner: reports grants and personal fees from Vifor, personal fees from Pfizer, personal fees from Boehringer Ingelheim, personal fees and non-financial support from Sphingotec, grants from ZS Pharma, personal fees from Bayer, personal fees from Medtronic, outside the submitted work; Petr Widimsky: none; Thomas Gremmel: reports personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Boehringer-Ingelheim, personal fees from Bristol Myers Squibb, personal fees from Pfizer, outside the submitted work; Juan Carlos Kaski: reports personal fees from Bayer UK, outside the submitted work; Gianluigi Savarese: reports grants and personal fees from Vifor, grants and personal fees from Boehringer Ingelheim, grants and personal fees from AstraZeneca, personal fees from Roche, outside the submitted work; Giuseppe M.C. Rosano: none; Claudio Borghi: none; Keld Kjeldsen: none; Christian Torp-Pedersen: reports grants from Bayer, outside the submitted work; Thomas Andersen Schmidt: none. Basil S. Lewis: reports grants and personal fees from BMS, personal fees from Pfizer, grants from Boehringer-Ingelheim, grants from Daiichi-Sankyo, grants from Bayer Healthcare, during the conduct of the study. Heinz Drexel: none; Juan Tamargo: none; Dan Atar: reports personal fees from Boehringer-Ingelheim, grants and personal fees from BMS/Pfizer, personal

fees from MSD, personal fees from Bayer, personal fees from Astra-Zeneca, personal fees from Sanofi, grants from Medtronic, outside the submitted work; Stefan Agewall: none; Alexander Niessner: reports personal fees from Bayer, personal fees from BMS, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Daiichi Sankyo, personal fees from Pfizer, outside the submitted work.

References

1. Krijthe BP, Kunst A, Benjamin EJ et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013; 34: 2746–51
2. Björck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke*. 2013 Nov;44(11):3103-8.
3. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;34: 2746–2751.
4. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;6:213–220.
5. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016 Oct 7;37(38):2893-2962.
6. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S; Task Force on Practice Guidelines, American College of Cardiology/American Heart Association; Committee for Practice Guidelines, European Society of Cardiology; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J*. 2006 Aug;27(16):1979-2030.
7. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010 Oct;31(19):2369-429. doi: 10.1093/eurheartj/ehq278. Epub 2010 Aug 29. No abstract available. Erratum in: *Eur Heart J*. 2011 May;32(9):1172.
8. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010 Feb;137(2):263-72. doi: 10.1378/chest.09-1584. Epub 2009 Sep 17.
9. Goto S, Merrill P, Wallentin L, Wojdyla DM, Hanna M4, Avezum A, Easton JD, Harjola VP, Huber K, Lewis BS, Parkhomenko A, Zhu J, Granger CB, Lopes RD, Alexander JH. Antithrombotic therapy use and clinical outcomes following thrombo-embolic events in patients with atrial fibrillation: insights from ARISTOTLE. *Eur Heart J Cardiovasc Pharmacother*. 2018 Apr 1;4(2):75-81.
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel userfriendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093–1100.

11. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke*. 2010 Dec;41(12):2731-8. doi: 10.1161/STROKEAHA.110.590257. Epub 2010 Oct 21.
12. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. *J Am Coll Cardiol*. 2015 Jan 27;65(3):225-32. doi: 10.1016/j.jacc.2014.10.052.
13. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J, Siegbahn A, Stewart RA, White HD, Granger CB, Wallentin L on behalf of the ARISTOTLE and STABILITY Investigators. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;37:1582-1590.
14. Emily C. O'Brien, DaJuanicia N. Simon, Laine E. Thomas, Elaine M. Hylek, Bernard J. Gersh, Jack E. Ansell, Peter R. Kowey, Kenneth W. Mahaffey, Paul Chang, Gregg C. Fonarow, Michael J. Pencina, Jonathan P. Piccini, Eric D. Peterson; The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;36:3258–3264.
15. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE . A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;58:395–401.
16. Roldan V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, Vicente V, Lip GY. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a 'real-world' population with atrial fibrillation receiving anticoagulant therapy. *Chest* 2013;143:179–184.
17. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMOR- R(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fib- rillation) study. *J Am Coll Cardiol* 2012;60:861–867.
18. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldles M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–992.
19. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.
20. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–891.
21. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinaz J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I,

- Hanyok JJ, Mercuri M, Antman EM, Investigators EA-T. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–2104.
22. Hagii J, Tomita H, Metoki N, Saito S, Shioto H, Hitomi H, Kamada T, Seino S, Takahashi K, Baba Y, Sasaki S, Uchizawa T, Iwata M, Matsumoto S, Osanai T, Yasujima M, Okumura K. Characteristics of intracerebral hemorrhage during rivaroxaban treatment: comparison with those during warfarin. *Stroke* 2014;45: 2805–2807.
 23. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation*. 2012 May 15;125(19):2298-307.
 24. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol*. 2015 Feb 24;65(7):635-42. doi: 10.1016/j.jacc.2014.11.046.
 25. Fangel MV, Nielsen PB, Larsen TB, Christensen B, Overvad TF, Lip GYH, Goldhaber SZ, Jensen MB. Type 1 versus type 2 diabetes and thromboembolic risk in patients with atrial fibrillation: A Danish nationwide cohort study. *Int J Cardiol*. 2018 Oct 1;268:137-142.
 26. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: A nationwide cohort study of 9519 patients. *Int J Cardiol* 2014;177:91–99.
 27. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005;112:1687–1691.
 28. Mikkelsen AP, Lindhardsen J, Lip GY, Gislason GH, Torp-Pedersen C, Olesen JB. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. *J Thromb Haemost*. 2012 Sep;10(9):1745-51. doi: 10.1111/j.1538-7836.2012.04853.x.
 29. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500–1510.
 30. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Granger CB, Wallentin L, ARISTOTLE and RE-LY Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016; 387:2302–2311.
 31. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Siegbahn A, Yusuf S, Wallentin L. Importance of persistent elevation of cardiac biomarkers in atrial fibrillation: a RE-LY substudy. *Heart*. 2014 Aug;100(15):1193-200.
 32. Ishii M, Ogawa H, Unoki T, An Y, Iguchi M, Masunaga N, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Akao M. Relationship of Hypertension and Systolic Blood Pressure With the Risk of Stroke or Bleeding in Patients With Atrial Fibrillation: The Fushimi AF Registry. *Am J Hypertens*. 2017 Nov 1;30(11):1073-1082.

33. Hamatani Y, Ogawa H, Uozumi R, Iguchi M, Yamashita Y, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Morita S, Akao M. Low Body Weight Is Associated With the Incidence of Stroke in Atrial Fibrillation Patients - Insight From the Fushimi AF Registry. *Circ J* 2015;79(5):1009-17
34. Tittel L, Endig S, Marten S, Reitter A, Beyer-Westendorf I, Beyer-Westendorf J. Impact of BMI on clinical outcomes of NOAC therapy in daily care - Results of the prospective Dresden NOAC Registry (NCT01588119). *Int J Cardiol*. 2018 Jul 1;262:85-91.
35. El-Saifi N, Moyle W, Jones C, Tuffaha H. Medication Adherence in Older Patients With Dementia: A Systematic Literature Review. *J Pharm Pract*. 2018 Jun;31(3):322-334.
36. Zeng WT, Sun XT, Tang K, Mei WY, Liu LJ, Xu Q, Cheng YJ. Risk of thromboembolic events in atrial fibrillation with chronic kidney disease. *Stroke*. 2015 Jan;46(1):157-63.
37. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R₂CHADS₂ index in the ROCKET AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study cohorts. *Circulation*. 2013;127:224-32.
38. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc*. 2013;2:e000250.
39. Herring N, Page SP, Ahmed M, Burg MR, Hunter RJ, Earley MJ, Sporton SC, Newton JD, Sabharwal NK, Myerson SG, Bashir Y, Betts TR, Schilling RJ, Rajappan K. The Prevalence of Low Left Atrial Appendage Emptying Velocity and Thrombus in Patients Undergoing Catheter Ablation for Atrial Fibrillation on Uninterrupted Peri-procedural Warfarin Therapy. *J Atr Fibrillation*. 2013 Apr 6;5(6):761.
40. Santiago D, Warshofsky M, Li Mandri G, Di Tullio M, Coromilas J, Reiffel J, Homma S. Left atrial appendage function and thrombus formation in atrial fibrillation-flutter: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 1994 Jul;24(1):159-64.
41. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol*. 2015 May 26;65(20):2239-51.
42. Anaissie J, Monlezun D, Seelochan A, Siegler JE, Chavez-Keatts M, Tiu J, Pineda D, George A, Shaban A, Abi Rafeh N, Schluter L, Martin-Schild S, El Khoury R. Left Atrial Enlargement on Transthoracic Echocardiography Predicts Left Atrial Thrombus on Transesophageal Echocardiography in Ischemic Stroke Patients. *Biomed Res Int*. 2016;2016:7194676.
43. Gupta DK, Shah AM, Giugliano RP, Ruff CT, Antman EM, Grip LT, Deenadayalu N, Hoffman E, Patel I, Shi M, Mercuri M, Mitrovic V, Braunwald E, Solomon SD; Effective aNticoagulation with factor xA next GEneration in AF-Thrombolysis In Myocardial Infarction 48 Echocardiographic Study Investigators. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. *Eur Heart J*. 2014 Jun 7;35(22):1457-65
44. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Díaz R, Hohnloser SH, Lewis BS, Shestakovska O, Wang J, Connolly SJ. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J*. 2015 Feb 1;36(5):281-7a.

45. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J*. 2016 May 21;37(20):1591-602.
46. Scardi S, Mazzone C, Pandullo C, Goldstein D, Poletti A, Humar F. Loneatrialfibril- lation: prognostic differences between paroxysmal and chronic forms after 10 years of follow-up. *Am Heart J* 1999;137(4 Pt 1):686-691.
47. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Interv Card Electrophysiol*. 2000 Jun;4(2):369-82
48. Flaker GC, Belew K, Beckman K, Vidaillet H, Kron J, Safford R, Mickel M, Barrell P; AFFIRM Investigators. Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J*. 2005 Apr;149(4):657-63.
49. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA; MOST Investigators. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MDe Selection Trial (MOST). *Circulation*. 2003 Apr 1;107(12):1614-9.
50. Roldan V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, Vicente V, Lip GY. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a 'real-world' population with atrial fibrillation receiving anticoagulant therapy. *Chest* 2013;143:179-184.
51. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol* 2011;57:173-180.
52. Lip GY, Skjøth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *J Am Coll Cardiol*. 2015 Apr 14;65(14):1385-94.
53. Flaker GC, Eikelboom JW, Shestakovska O, Connolly SJ, Kaatz S, Budaj A, Husted S, Yusuf S, Lip GY, Hart RG. Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. *Stroke* 2012;43:3291-3297.
54. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanus-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011 Mar 3;364(9):806-17.
55. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2011 Jan 1;4(1):14-21.
56. Lopes RD, Al-Khatib SM, Wallentin L, Yang H, Ansell J, Bahit MC, De Caterina R, Dorian P, Easton JD, Erol C, Ezekowitz JA, Gersh BJ, Granger CB, Hohnloser SH, Horowitz J, Hylek EM, McMurray JJ, Mohan P, Vinereanu D, Alexander JH. Efficacy and safety of apixaban compared with warfarin according

to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet*. 2012 Nov 17;380(9855):1749-58.

57. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. *N Engl J Med* 2010;363:1875–1876.
58. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, Singer DE. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007;120:700–705.
59. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH; RE-DUAL PCI Steering Committee and Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med*. 2017 Oct 19;377(16):1513-1524.
60. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med*. 2016 Dec 22;375(25):2423-2434.
61. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH; AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med*. 2019 Mar 17. doi: 10.1056/NEJMoa1817083. [Epub ahead of print]
62. Gomez-Outes A, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus warfarin in patients with nonvalvular atrial fibrillation: a systematic review and meta-analysis of subgroups. *Thrombosis* 2013;2013:640723.
63. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383: 955–962.
64. Coleman CI, Turpie AGG, Bunz TJ, Eriksson D, Sood NA, Baker WL. Effectiveness and Safety of Rivaroxaban Versus Warfarin in Nonvalvular Atrial fibrillation Patients with a Non-Sex-Related CHA2DS2-VASc Score of 1. *Eur Heart J Cardiovasc Pharmacother*. 2018 Jul 17. doi: 10.1093/ehjcvp/pvy025. [Epub ahead of print]

Table Legends

Table 1: Event rates within categories of CHA₂DS₂-VASc and HAS-BLED score. Adjusted event rates within categories of CHA₂DS₂-VASc Score and HAS-BLED Score. Data obtained via Pisters R (CHEST, 2010), Lip GYH (CHEST, 2010), Lip GYH (Stroke, 2010) – Euro Heart Survey (8-10)

Table 2: Values for individual risk stratification. Values that favor oral anticoagulation and allow individual thromboembolic risk stratification in AF patients with a CHA₂DS₂-Vasc of 1. eGFR = estimated Glomerular Filtration Rate; LA = Left Atrium; LAA = Left Atrial Appendage; Nt-proBNP = N-terminal pro-B-type natriuretic peptide.

Figure Legends

Figure 1: Decision tree for OAC in patients with AF and a CHA₂DS₂-VASc score of 1. NOAC = non-Vitamin K antagonist oral anticoagulants; OAC = Oral Anticoagulation; VKA = Vitamin K Antagonist.

Table 1: Event rates within categories of CHA₂DS₂-VASc and HAS-BLED score.

CHA ₂ DS ₂ -VASc score		HAS-BLED score	
Category	Thromboembolic event rate/year	Category	Bleeding event rate/year
0	0	0	0.59 – 1.13
1	0.6 – 1.3	1	1.02 – 1.51
2	1.6 – 2.2	2	1.88 – 3.20
3	3.2 – 3.9	3	3.74 – 19.51
4	1.9 – 4.0	4	8.70 – 21.43
5	3.2 – 6.7		
6	3.6 – 9.8		
7	8.0 – 9.6		
8	6.7 – 11.1		
9	>15.2		

Table 1: Adjusted event rates within categories of CHA₂DS₂-VASc Score and HAS-BLED Score. Data obtained via Pisters R (CHEST, 2010), Lip GYH (CHEST, 2010), Lip GYH (Stroke, 2010) – Euro Heart Survey (8-10)

Table 2: Values for individual risk stratification

Favors oral anticoagulation (in case of low bleeding risk)
Age (>65 years)
Type II diabetes mellitus
Atrial fibrillation (not atrial flutter)
Persistent/permanent atrial fibrillation

Additional factors for thromboembolic risk modification
Obesity (body mass index ≥30)
Proteinuria (>150mg/24h or equivalent)
eGFR (<45ml/h)
NT-proBNP (>1400ng/l)
Positive cardiac troponin T and I
Enlarged LA volume (≥73mL) or diameter (≥4.7cm)
LAA emptying velocity (<20cm/s)
ABC (Age/Biomarker/Clinical history) score

Table 2: Values for individual risk stratification: Values that favor oral anticoagulation and allow individual thromboembolic risk stratification in patients with a CHA₂DS₂-Vasc of 1. eGFR = estimated Glomerular Filtration Rate; LA = Left Atrium; LAA = Left Atrial Appendage; Nt-proBNP = N-terminal pro-B-type natriuretic peptide

Figure 1

